

REMARKS

Claims 1-13 are pending in the application. Claims 1-3 and 6-10 are withdrawn in response to the prior restriction requirement. In the Office Action mailed February 22, 2007, the specification is objected to because the drawing numbers are not correctly referred to in the Brief Description of the Drawings. Claims 11 and 12 are rejected under 35 U.S.C. 112, second paragraph as being indefinite. Claims 4 and 5 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,939,973 (Bass et al., hereinafter "Bass"). Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Reynolds in view of U.S. Pat. No. 7,062,385 (White et al., hereinafter "White").

I. Objections to Specification

The Specification is objected to because the drawing numbers are not correctly referred to in the Brief Description of the Drawings. The Applicants have herein amended the Specification to correctly reference the drawing numbers and to correct typographical errors noticed by the Applicants. No new matter is added by these amendments. Entry of these amendments and withdrawal of the objection to the Specification is therefore respectfully requested.

II. Rejections under 35 U.S.C. 112, second paragraph

Claims 11 and 12 are rejected under 35 U.S.C. 112, second paragraph as being indefinite. In particular, claim 11 is rejected as being indefinite because "it is unclear how monitoring the deprotection of the 5' protecting group is related to employing a channel opening." The Applicants have herein amended claim 11 to recite substeps of the step of monitoring the deprotection of the 5' protecting group, which substeps clarify how monitoring the deprotection of the 5' protecting group is related to employing a channel opening. The Applicants have further amended independent claim 5, from which claim 11 depends, to clarify that the step of detecting errors is based on results from the step of monitoring. Support for these amendments is found in the Specification at least at paragraphs [0030] and [0136], and in Fig. 14B. No new matter is added by this amendment. The Applicants respectfully note that the description in the Office Action (2/22/2007 Office Action, paragraph 5) of what the specification discloses is related to the aspect of the invention presently claimed in independent claim 4 (and described in paragraphs [0029] and [00135] and Fig. 14A), not to the aspect claimed in independent claim 5,

which aspect is fully described and supported in the Specification by at least the paragraphs and drawing noted above. Entry of the amendment and withdrawal of the rejection of claim 11, as amended, is therefore respectfully requested.

Claim 12 is rejected as being indefinite for having insufficient antecedent basis for the limitations “the force” and “the growing nucleic acid molecule.” The Applicants have herein amended claim 12 to correct the claim language so that the recited limitations have proper antecedent basis and to correctly depend from claim 4. Support for these amendments is found in the Specification at least at paragraphs [0022], [0118]-[0120], and [0135], in Figs. 9A and 9B, and in original claim 6. No new matter is added by this amendment. The Applicants apologize for any confusion which the typographical error that led to the incorrect dependency claim may have caused and acknowledge that the problem of lack of antecedent basis arose in large part from this defect. Entry of the amendment and withdrawal of the rejection of claim 12, as amended, is therefore respectfully requested.

III. Rejections under 35 U.S.C. 102(e)

Claims 4 and 5 are rejected under 35 U.S.C. 102(e) as being anticipated by Bass. The Applicants respectfully traverse the rejections. In the Applicants’ invention, errors in the sequence of the newly created nucleic acid are detected and corrected using the claimed methods. The methods of the Applicants detect all types of sequence errors, including addition of the wrong base, insertion errors (addition of too multiples of an intended base), and deletion errors (omission of an intended base). Bass does not teach the invention of the Applicants, as *Bass fails to teach the detection and correction of errors in the sequence of the newly synthesized nucleic acid.*

In contrast to the Applicants, Bass merely teaches detection of errors in the process of reagent delivery, in particular, Bass detects whether or not a droplet has actually been delivered. Bass makes the assumption that, if a reagent is properly delivered, then the appropriate bond is formed. The method of Bass does not confirm that the right sequence has been made, rather it just determines whether all that can be done has been done to ensure that the right sequence is made. The invention of the Applicants, in contrast, does not just detect whether the correct base *could have been added*, but in fact detects whether it has *actually been added* and *whether that addition is correct*. The Applicants therefore are actually monitoring sequence fidelity, not just the possibility thereof, as is taught by Bass.

Two example scenarios can be described to illustrate some of the many ways in which this fundamental difference may manifest itself. In one example, even though a droplet is properly dispensed, no reaction occurs, resulting in a deletion error (the most common in phosphoramidite synthesis). In this scenario, Bass would assume that the sequence is correct and move on to the next reaction. In contrast, using the invention of the Applicants, it would be detected that the sequence was not correct and the reaction would be repeated before proceeding to the next reaction. In a second scenario, the droplet is properly dispensed but contamination leads to the wrong based being added or to multiple incorporations (insertion error). Once again, Bass assumes that the sequence is correct. If the invention of the Applicants is employed with multiple colored protecting groups (i.e. a different color for each base A, G, T, C), then whether the correct base has been incorporated can be determined by which color is detected and whether there are insertion errors can be determined by the color intensity being too high.

In order to clarify and to more distinctly claim and point out this aspect of the Applicants' invention, the Applicants have herein amended independent claims 4 and 5 in order to recite that the steps of detecting and correcting errors are directed to detecting and correcting errors in the sequence of the newly synthesized nucleic acid. Support for this amendment is found throughout the Specification, and particularly at least at paragraphs [0029], [0030] and [0134]-[0136], and in Figs. 14A and 14B. No new matter is added by these amendments, entry of which is therefore respectfully requested.

As discussed above, *detection and correction of errors in the sequence of the newly synthesized nucleic acid* is not shown in Bass. This deficiency of Bass is not cured by White or any other art of record, none of which teach *detection and correction of errors in the sequence of the newly synthesized nucleic acid*, in combination with the other claimed elements of the Applicants invention, as recited in currently amended independent claims 4 and 5 of the Applicants. Bass therefore fails to anticipate or make obvious the Applicants' invention, whether taken alone or in combination, as does all other art of record. Reconsideration and withdrawal of the rejections of claims 4 and 5 over Bass is therefore respectfully requested.

IV. Rejections under 35 U.S.C. 103(a)

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bass in view of White. The Applicants respectfully traverse the rejection. As discussed in the previous section, Bass fails to teach *detection and correction of errors in the sequence of the newly synthesized*

nucleic acid. These deficiencies of Bass are not cured by White or any other art of record.

Because White fails to cure the deficiencies of Bass, Bass in view of White therefore fail to make obvious the Applicants' invention. Reconsideration and withdrawal of the rejection of claim 13 is therefore respectfully requested.

Furthermore, because claim 13 depends from currently amended independent claim 5, which is in condition for allowance, claim 13 is also in condition for allowance. Reconsideration and withdrawal of the rejection of claim 13 is therefore also respectfully requested.

V. New claims

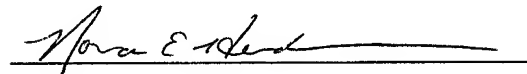
New dependent claims 14-18 have been added. New claim 14 is dependent on claim 4 and recites the use of the methods of claims 4 and 5 in combination. Support for new claim 14 is found at least at paragraphs [0029]-[0030] and [0134]-[0136], Figs. 14A and 14B, and original claim 5. New claim 15 is dependent on claim 4 and recites the combination of the method of new claim 14 with the step of claim 12. Support for new claim 15 is found at least at [0022], [0118]-[0120], and [0135], in Figs. 9A and 9B, and in original claim 6. New claim 16 is dependent on claim 4 and recites the step of claim 13 as applied to the method of claim 4. Support for new claim 16 is found at least at paragraphs [0026]-[0027] and [0125]-[0130], in Figs. 11A-B and 12A-B, and in original claim 7. New claims 17 and 18 are dependent on claims 4 and 5, respectively, and recite specifically some of the types of errors in sequence that may be detected and corrected using the invention of the Applicants. The types of sequence errors that occur during nucleic acid synthesis are well-known in the art of the invention, and support for new claims 17 and 18 is further found at least at paragraphs [0029], [0030], and [0134]-[0136], Figs. 14A and 14B. No new matter is added by these new claims. Entry of new claims 14-18 is therefore respectfully requested.

As discussed in Section III, Bass fails to teach *detection and correction of errors in the sequence of the newly synthesized nucleic acid*, as recited in currently amended independent claims 4 and 5 of the Applicants. These deficiencies of Bass are not cured by White or any other art of record. Because new claims 14-18 depend from independent claims 4 and 5, which are in condition for allowance, claims 14-18 are also in condition for allowance. Allowance of new claims 14-18 is therefore respectfully requested.

VI. Conclusion

Claims 4, 5, 11, and 12 have been amended. New claims 14-18 have been added. No new matter is presented by these amendments. The Applicants respectfully submit that claims 4, 5, and 11-18 are now in condition for allowance, which action is now requested. For this reason, and in view of the foregoing arguments, the Applicants believe that this application is now in condition for allowance, which action is respectfully solicited. Should there remain any unresolved issues, it is respectfully requested that the Examiner telephone Norma E. Henderson, Applicants' Attorney, at 603-437-4400, so that such issues may be resolved as expeditiously as possible.

Respectfully Submitted,



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Date

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